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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/659,178	09/09/2003	David Jonathan Madge	2451.0020006	7469

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EXAMINER	
VALENROD, YEVGENY	
ART UNIT	PAPER NUMBER
1621	

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01/31/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/659,178	MADGE ET AL.	
	Examiner	Art Unit	
	Yevgeny Valenrod	1621	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 December 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-23,26-55,57 and 59-71* is/are pending in the application.

4a) Of the above claim(s) *29* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-23,26-28,30-55,57 and 59-71* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *09 September 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *See Continuation Sheet*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Attachment(s) 3). Information Disclosure Statement(s) (PTO/SB/08), Paper No(s)/Mail Date :12/05/07, 10/22/07, 10/16/07, 9/18/07.

DETAILED ACTION

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-18, 21, 22, 23, 26-28, 30-36, 39-43, 47-51, 66-68, 71 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rewinkel et al. (Current Pharmaceutical Design, 1999, 5, 1043-1075) in view of de Nanteuil et al. (US 5,814,622) and in further view of Adams et al. US 5,780,454).

Instant claims 1-18, 21, 22, 23, 26-28 and 30-36 are directed to a pharmaceutically acceptable base addition salt of a boronic acid of formula (I) in claim 1, or formula (II) in claim 14 and to formulation of the said salt in claims 26-28.

Scope of prior art

Rewinkel et al. teach a compound of formula 21 (page 1052, bottom left of Table 3). The said compound is a boronic acid that has the methoxyalkyl substituent for R^9 in the instant claim 1, a Pro amino acid residue, which satisfies the structural limitation of claim 17, a hydrophobic moiety presented by the diphenylalanine residue, and a protected N-terminal amine group. Renkwel et al.

Provide Ki for thrombin inhibition in the table on the bottom of page 1052. Compound 21, has Ki of 14 nM, which is below 100nM as claimed in claims 7 and 28.

Ascertaining the difference between prior art and the instant claims

Rewinkel et al. teach the organic component of the instantly claimed organoboronic acid salt. They also teach the boronic acid attached to the organic component in a position consistent with the structural limitations of the instant claims. However, they fail to teach the pharmaceutically acceptable salt of the boronic acid.

Secondary references

Nanteuil et al. describe compound of formula (I/g) (organoboronic acid) and pharmaceutically acceptable salts thereof (column 6, lines 20-36). The pharmaceutically acceptable salts include both base and acid addition salts. In Column 3, lines 32-34 Nanteuil et al. describe examples of counterions for base addition salts. Said examples include Sodium, Potassium and amines.

Adams et al. teach boronic acid compounds of formula 1(a) which encompass the instantly claimed compounds. Adams et al. also teach pharmaceutically acceptable base addition salts (column 9, lines 47-48) which include various alkaline metal, alkaline earth metal and amine (including amino acids) salts (column 9 lines57-65).

Motivation and obviousness

It is obvious to form salts from known acids. In re Williams, 89 USPQ 396 (CCPA 1951). Rewinkel et al. teach compound 21, which is the acid of the instantly claimed pharmaceutically acceptable salt. At the time the instant invention was made, one of ordinary skill in the art looking to alter the permeability, solubility, or other physiological properties commonly associated with producing pharmaceutically acceptable salts of known acid (see Davies et al, The pharmaceutical journal, 2001, Vol 266, p 322-323; particularly page 322, column 1, first paragraph) would have been motivated to prepare a salt of the organoboronic acid 21 described by Rewinkel et al. Such a modification would not be new to the art. Nanteuil et al. describe pharmaceutically acceptable salts of organoboronic acids and thus provide an expectation of success for performing the said modification. Nanteuil et al. do not limit themselves to the counterion examples that are listed in column 3 lines 32-34. They specifically mention that these examples are provided without any limitation. One of ordinary skill in the art would be motivated to produce various pharmaceutically acceptable salts in order to achieve the desired properties of the pharmaceutical agent. Pharmaceutically acceptable salts of organoboronic acids salts include alkaline metal salts, alkaline earth metal salts (including calcium) and amine salts (Adams et al. US 5,780,454; column 9, lines 57-65). In the absence of some unexpected properties for the base addition salts of organoboronic acids of the instantly claimed compounds, the invention is seen to be prima facie obvious in view of the prior art of record and the case law cited herein.

Reply to applicants' remarks

Applicant draws attention to the Wu et al. reference. Said reference is also discussed in Dr. Kennedy's declaration. Wu provides a single example of a peptide boronic acid is not stable in alkaline conditions which are required for production of the salts of the instant invention. According to the applicant one of ordinary skill in the art would not be motivated to make base addition salt of boronic acids in view of the teachings of Wu et al. This argument is not found persuasive. Wu only provides experimental data for a single compound that does not fall within the scope of the instant invention with a single base, NaOH. Adams on the other hand suggests making boronic acid salts that do fall within the scope of the instant invention and teaches using a variety of salts, not only the sodium salt.

Applicant states and Dr. Kennedy declares that boronic acids are unlike carboxylic acids. Boronic acids are prone to degradation, while the carboxylic acids are relatively stable. Examiner recognizes the chemical and physical differences between boronic acids and carboxylic acids. The instability of boronic acids provides motivation for one of ordinary skill in the arts to find a more stable analogue. Although it is more common in the art to stabilize the boronic acids via diester analogues, Adams suggests making salts for pharmaceutical applications. One of ordinary skill in the art would therefore chose from the two available options in order to affect stability or other chemical or physiological properties of the boronic acids. The Gupta reference referred to

on page 5 of the "Remarks" solves the instability issue by making the ester. Gupta does provide a teaching away from making the salt.

Applicant also argues and Dr. Kennedy declares that Rewinkel teaches an incorrect structure for compound 21 (Page 6 of the Remarks). The cited reference (Deadman et al.) in fact does not teach the free acid but rather an ester. One of ordinary skill would recognize that Rewinkel provides the active ingredient as boronic acid and Deadman provides the protected Boronic acid. With the teaching of Rewinkel and Adams, one of ordinary skill in the art would be free to chose from either preparing the salt as Adams teaches, or preparing an Ester as Deadman teaches. The combination of Riwinkel and Adams is still sufficient to make a *prima facia* case for obviousness.

Examiner acknowledges that De Nanteuil and Adams fail to provide examples where the base addition salts are actually made (see page 7 of remarks). However, both teach the salts of a wide variety of boronic acids which is sufficient for the obviousness rejection. Applicant on the other hand has provided only one reference where a specific compound decomposes under specific conditions. Although preparation of boronic acid salts might be difficult to accomplish, it's not sufficient to overcome a teaching directed to their preparation.

Double Patenting

Claims 1-23, 26-28 and 30-55, 57, 59-71 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over

claims 1-21, 23, 25, 50-56 and 71-73 of U.S. Patent No. 7,112,572 ('572). Although the conflicting claims are not identical, they are not patentably distinct from each other because the all the limitations of the instant claims are found in the sited claims of ('572).

Instant claims are directed to a pharmaceutically acceptable base addition salt of a boronic acid of formula (I) in claim 1, or formula (II) in claim 14, to formulation of the said salt in claims 26-28, pharmaceutical formulations in claims 50-56, anhydride comprising salts in claims 71-73.

Claim 2 of '572 claims a structure that encompasses the structure of the instant claim 1. Claim 12 of '572 displays a structure that is identical compound of formula (II) in the instant claim 14. Claims of '572 that directed to a salt and are dependent on claims 2 and 12 have all of the limitations of the instant claims 1-23 and 30-38. The formulations and medicament claimed in the instant claims 26-28 are obvious over claims 20, 23 and 25 of '572. The said formulation and medicament claims differ from the instant invention in that the compounds from which the formulation and medicament is made are not identical to the compound in '572. However, compound (III) of '572 encompasses all of the instantly claimed compounds, and compound (IV) of '572 is specie of the instantly claimed compound (I).

Conclusion

Claims 1-23, 26-55, 57, 59-71 are pending

Claim 29 is withdrawn

Clams 1-23, 26-28 and 30-55, 57, 59-71 are rejected

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Yevgeny Valenrod whose telephone number is 571-272-9049. The examiner can normally be reached on 8:30am-5:00pm M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler can be reached on 571-272-0871. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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